सत्यमेव जयते

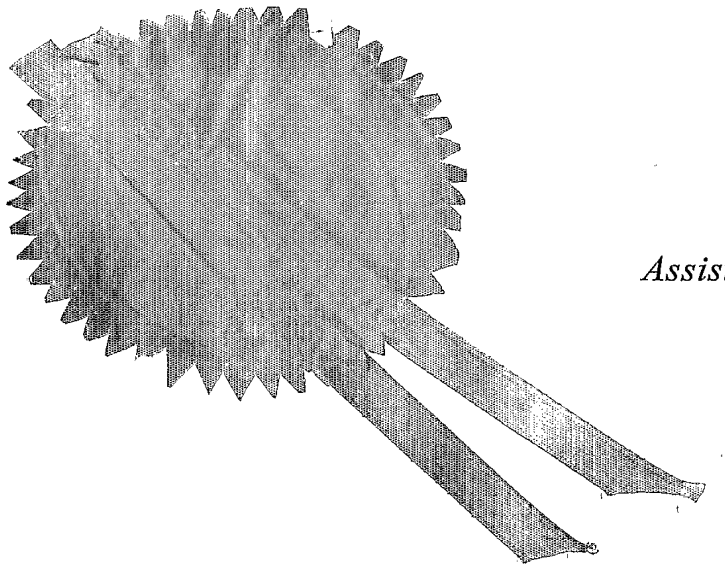
INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

IB/05/420

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.****237/Del/2004*** *dated* ***19th February 2004****.*

Witness my hand this 2nd day of May 2005.



(S.K. PANGASA)
Assistant Controller of Patents & Designs

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0237-04

FORM 1

19 FEB 2004

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR PREPARATION OF AN EXTENDED RELEASE FORMULATION OF DIVALPROEX"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. PRATIK KUMAR
b. GIRISH KUMAR JAIN
c. ASHOK RAMPAL

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

9. Following declaration was given by the inventors or applicants in the convention country:

We, PRATIK KUMAR, GIRISH KUMAR JAIN, ASHOK RAMPAL of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19 Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(PRATIK KUMAR)

b.

(GIRISH KUMAR JAIN)

c.

(ASHOK RAMPAL)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Complete Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.**3,000/-** (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **17TH** day of **February, 2004.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR PREPARATION OF AN EXTENDED RELEASE FORMULATION OF DIVALPROEX

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention concerns a process for preparation of an extended release formulation comprising valproic acid, a pharmaceutically acceptable salt, ester, or amide thereof or divalproex sodium.

Valproic acid, 2-propylpentanoic acid, and its derivatives are widely used in the treatment of mania, migraine and epilepsy. After ingestion, they dissociate into gastrointestinal tract to valproate ion, which on absorption produce the desired effect.

Valproic acid and its derivative have few serious shortcomings associated with them. They are either liquid or liquify rapidly and are sticky. Further, most of them are extremely hygroscopic in nature. These physicochemical properties pose serious problems during manufacture of pharmaceutical compositions, demanding well-defined approaches to overcome these drawbacks.

Besides, they also suffer from relatively short elimination half-lives. For example, a short half-life of 6–17 hours in adults and 4–14 hours in children for valproic acid has been reported. Frequent dosing is thus necessary to maintain reasonably stable plasma concentrations. However, it results in inconvenience to the patient, leading to poor compliance. Moreover, widely fluctuating plasma concentrations of the drug also result in administration of erratic amounts of drug.

A solution to the above problem is an extended release formulation of divalproex sodium that permits once a day dosing and thereby helps in maintaining a reasonably stable plasma concentration.

Abbott in its US patent 6,419,953 describes an extended release matrix tablet comprising a valproate compound; hydroxypropyl methylcellulose; lactose, microcrystalline cellulose, and silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns. The patent further teaches that addition of either 1% silicon dioxide or/and 5%

microcrystalline cellulose to the hydrophilic matrix formulations of the invention doubles tablet hardness. However the problem of sticking still persists when conventionally used grades of silicon dioxide are employed, and can be overcome only by the use of special grade silicon dioxide (Syloid® 244) having a smaller average particle size ranging from about 1 micron to about 10 microns.

The inventors have developed a pharmaceutical composition for oral administration comprising a drug capable of dissociating to produce valproate ion, and low and high viscosity grade hydroxypropyl methylcellulose. The inventors have found out that low viscosity grade helps in maintaining the integrity of the matrix, thereby playing an important role in controlling the release of the drug from the matrix.

The extended release pharmaceutical composition provides the drug over a prolonged period of time in such a manner as to provide substantial level of plasma concentrations of the drug following once-a-day dosing.

In one general aspect, there is provided an extended release pharmaceutical composition comprising

a) a drug capable of dissociating to produce valproate ion;
b) from 15-50% of a high viscosity grade hydroxypropyl methylcellulose ;
c) from 0.1-10% of a low viscosity grade hydroxypropyl methylcellulose.

In another general aspect, there is provided a process for the preparation of an extended release pharmaceutical composition comprising the steps of-

a) blending a drug capable of dissociating as valproate ion, from 15-50% w/w of a high viscosity grade hydroxypropyl methylcellulose and from 0.1-10% w/w of a low viscosity grade hydroxypropyl methylcellulose,
b) optionally granulating the blend,
c) lubricating the blend of step a) or granules of step b), and

d) compressing into or filling into suitable size solid dosage form.

The process includes a) blending a drug capable of dissociating as valproate ion, high viscosity grade hydroxypropyl methylcellulose and low viscosity grade hydroxypropyl methylcellulose, b) optionally granulating the blend, c) lubricating the blend of step a) or granules of step b), and d) compressing into or filling into suitable size solid dosage form.

In a yet another embodiment, there is provided a method of treating mania, migraine and epilepsy using an extended release pharmaceutical composition comprising an extended release pharmaceutical composition comprising

a) a drug capable of dissociating to produce valproate ion;

b) from 15-50% of high viscosity grade hydroxypropyl methylcellulose ;

c) from 0.1-10% of low viscosity grade hydroxypropyl methylcellulose.

In one general aspect, there is provided an extended release pharmaceutical composition comprising

a) a drug capable of dissociating to produce valproate ion;

b) from 15-50% of a high viscosity grade hydroxypropyl methylcellulose ;

c) from 0.1-10% of a low viscosity grade hydroxypropyl methylcellulose

wherein the composition is free of microcrystalline cellulose.

In another general aspect, there is provided a process for the preparation of an extended release pharmaceutical composition comprising

a) a drug capable of dissociating to produce valproate ion;

b) from 15-50% of high viscosity grade hydroxypropyl methylcellulose ;

c) from 0.1-10% of low viscosity grade hydroxypropyl methylcellulose

wherein the composition is free of microcrystalline cellulose.

In another general aspect, there is provided a method of treating mania, migraine and epilepsy using an extended release pharmaceutical composition comprising

a) a drug capable of dissociating to produce valproate ion;

b) from 15-50% of high viscosity grade hydroxypropyl methylcellulose ;

c) from 0.1-10% of low viscosity grade hydroxypropyl methylcellulose

wherein the composition is free of microcrystalline cellulose.

The term 'pharmaceutical composition' as used herein includes solid dosage forms such as tablet, capsule, pill and like. The tablets can be prepared by techniques known in the art and contain a therapeutically useful amount of the valproate compound and such excipients as are necessary to form the tablet by such techniques. Tablets and pills can additionally be prepared with enteric coatings and other release-controlling coatings for the purpose of acid protection, easing swallow ability, etc.

The term 'drug capable of dissociating as valproate ion into the gastrointestinal tract' includes a compound which dissociates within the gastrointestinal tract to produce a valproate ion including, but not limited to, valproic acid, the sodium salt of valproate, divalproex sodium, any of the various salts of valproic acid described below, and any of the prodrugs of valproic acid described below.

Valproic acid is known for its activity as an antiepileptic compound as described in the Physician Desk Reference, 52nd Edition, page 421, 1998. Upon oral ingestion within the gastrointestinal tract, the acid moiety dissociates to form a carboxylate moiety (i.e. a valproate ion).

The sodium salt of valproic acid is also known in the art as an anti-epileptic agent. It is also known as sodium valproate and is described in detail in The Merck Index, 12 Edition, page 1691, (1996).

Divalproex sodium, sodium hydrogen divalproate, is effective as an antiepileptic agent and is also used for migraine and bipolar disorders. It is a stable co-ordination compound comprising of sodium valproate and valproic acid in a 1:1 ratio and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide may be used. The amount of drug may vary from about 10% to about 90% by weight of the total pharmaceutical composition weight. Like valproic acid, it also dissociates within the gastrointestinal tract to form a valproate ion.

In addition to these specific compounds, one of ordinary skill in the art would readily recognize that the carboxylic moiety of the valproate compound might be functionalized in a variety of ways. This includes forming compounds that readily metabolize in-vivo to produce valproate, such as valproate amide (valproimide), as well as other pharmaceutically acceptable amides and esters of the acid (i.e. prodrugs). This also includes forming a variety of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable basic addition salts include, but are not limited to cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Other possible compounds include pharmaceutically acceptable amides and esters. "Pharmaceutically acceptable ester" refers to those esters that retain, upon hydrolysis of the ester bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. The alcohol component of the ester will generally comprise (i) a C_2 -C_{12} aliphatic alcohol that can or can not contain one or more double bonds and can or can not contain branched carbons or (ii) a C_7 -C_{12} aromatic or heteroaromatic

alcohols. This invention also contemplates the use of those compositions, which are both esters as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

"Pharmaceutically acceptable amide" refers to those amides that retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. This invention also contemplates the use of those compositions, which are both amides as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

The term 'extended release pharmaceutical composition' as used herein includes any pharmaceutical composition that achieves the slow release of drug over an extended period of time, and includes both prolonged and controlled release compositions.

The extended release pharmaceutical composition may be prepared by processes known in the prior art for example, by comminuting, mixing, granulation, melting, sizing, filling, drying, molding, immersing, coating, compressing etc.

The term 'high viscosity grade hydroxypropyl methylcellulose' used herein includes grades of hydroxypropyl methylcellulose whose 2% w/w aqueous solution has nominal viscosity greater than about 10,000 cP.

The term 'low viscosity grade hydroxypropyl methylcellulose' used herein includes grades of hydroxypropyl methylcellulose whose 2% w/w aqueous solution has nominal viscosity less than about 1,000 cP.

Hydroxypropyl methylcellulose polymers which are hydrophilic in nature and which may be used in the present invention are of different viscosity grades such as those available under the brand name Methocel TM available from Dow Chemical Co. and Metolose from Shin Etsu Ltd. Examples of hydroxypropyl methylcellulose polymers having high viscosity include those

available under the brand names Methocel K15M, Methocel K100M, Methocel E10M, Metolose 90SH 15000 and Metolose 90SH 39000 whose 2% by weight aqueous solution have viscosities of 15,000 cP, 100,000 cP 10,000 cP, 15,000 cP and 39,000 cP, respectively. The high viscosity grade of hydroxypropyl methylcellulose polymers may be used in the concentration range of 15-50% w/w, in particular 20-40% w/w.

Examples of hydroxypropyl methylcellulose polymers of a low viscosity grade include those available under the brand names Methocel E5, Methocel E-15 LV, Methocel E50 LV, Methocel K100 LV Methocel F50 LV, Methocel E6LV, Methocel A15LV and Metolose 60SH 50, whose 2% by weight aqueous solutions have viscosities of 5 cP, 15 cP, 50 cP, 100 cP, 50 cP, 6cP, 15 cP, and 50 cP, respectively. The low viscosity grade of hydroxypropyl methylcellulose polymers may be used in the concentration range of 0.1-10% w/w, in particular 1-5% w/w.

In one general aspect, the extended release pharmaceutical composition may be prepared by wet granulation technique, comprising the steps of blending drug capable of dissociating as valproate ion in gastrointestinal tract, extended release polymer and optionally pharmaceutically inert excipient; granulating with a granulating fluid or solution/dispersion of binder; drying and sizing the granules; optionally blending with pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets and; optionally coating with film forming polymer and coating additives.

In one general aspect, the extended release pharmaceutical composition may be prepared by dry granulation technique, comprising the steps of blending drug capable of dissociating as valproate ion in gastrointestinal tract, extended release polymer and optionally pharmaceutically inert excipient; dry granulating the blend by roller compactor or slugging; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets and; optionally coating with film forming polymer and coating additives.

In another general aspect, the extended release pharmaceutical composition may be prepared by direct compression technique, comprising the steps of blending drug capable of dissociating as valproate ion in gastrointestinal tract, extended release polymer and optionally pharmaceutically inert excipient; lubricating the blend; directly compressing the lubricated blend into suitable sized tablets and; optionally coating with film forming polymer and coating additives.

In another general aspect, the extended release pharmaceutical composition may be prepared by melt extrusion technique, comprising the steps of blending drug capable of dissociating as valproate ion into gastrointestinal tract, extended release polymer and optionally pharmaceutically inert excipient; melting the blend followed by solidifying into a compact mass; breaking the compact mass into granules; optionally blending with pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend into suitable sized tablets and; optionally coating with film forming polymer and coating additives.

The term "pharmaceutically acceptable inert excipients" as used herein includes all excipients used in the art of manufacturing solid dosage forms. Examples include binders, diluents, surfactants, lubricants/glidants, coloring agents, and the like.

Specific examples of binders include methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Specific examples of diluents include calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and the like.

Surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Specific examples of lubricants/glidants include colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like.

Coloring agents include any FDA approved colors for oral use.

The pharmaceutical composition may optionally be coated with functional and/or non-functional layers comprising film-forming polymers, if desired.

Examples of film-forming polymers include ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit ® RL and RS; and the like. Alternatively, commercially

available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating.

The invention is further illustrated by the following examples, which is for illustrative purpose only and should not be considered as limiting the scope of invention in any way.

Divalproex sodium, lactose, Methocel K-15M CR and Methocel E-5 were blended in a rapid mixer granulator. The granules were prepared adding the granulation fluid (purified water) to mixture of drug/polymer/lactose. The resulting granules were dried in a fluidized bed drier and sieved through suitable sieves. The dried granules were blended with talc, colloidal silicon dioxide and magnesium stearate and compressed into suitable sized tablets and coated with an aqueous dispersion of PEG 400 and Opadry.

Table 1: Composition of extended release tablets of divalproex sodium.

Ingredients	**Wt/tablet (mg)** **Example 1**
Divalproex sodium	542.3
Lactose	90.0
Methocel K-15M CR	320.0
Methocel E-5	20.0
Water	q.s.
Magnesium Stearate	5.0
Talc	8.0
Colloidal Silicon Dioxide	17.0

***In vitro* dissolution study**

In vitro release of extended release tablets of divalproex sodium as per composition of example 1 was done in 900 ml phosphate buffer (pH 6.8) with 1% sodium lauryl sulphate in USP type II apparatus at a paddle speed of 100 rpm. The tablets were kept in sinker basket of 10#. The results are shown in table 2.

Table 2: Drug release profile of extended release formulation.

Time (hr)	Cumulative percentage of drug released from the formulation of example 1
1	16
2	27
4	35
8	53
12	69
16	78
20	92
24	102

While particular formulation has been described above, it will be apparent that various modifications and combinations of the formulations detailed in the text can be made without departing from the spirit and scope of the invention. For example, different concentration of high viscosity grade and low viscosity grade polymers as given in Table 3.

Table 3: Composition of extended release tablets of divalproex sodium (example 2 & 3).

Ingredients	Wt/tablet (mg) Example 2	Wt/tablet (mg) Example 3
Divalproex sodium	542.3	542.3
Lactose	90.0	90.0
Methocel K-15M CR	310.0	330.0
Methocel E-5	30.0	12.0
Water	q.s.	q.s.
Magnesium Stearate	5.0	5.0
Talc	8.0	8.0
Colloidal Silicon Dioxide	17.0	17.0

The extended release tablet formulations of the present invention thus provide an effective delivery system for the once daily administration of valproic acid (divalproex sodium) to patients in need of such treatment.

While there have been shown and described what are the preferred embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various modifications in the formulations and process can be made without departing from the scope of the invention as it is defined by the appended claims.

WE CLAIM:

1. A process for the preparation of an extended release pharmaceutical composition comprising the steps of-
   a) blending a drug capable of dissociating as valproate ion, from 15-50% w/w of a high viscosity grade hydroxypropyl methylcellulose and from 0.1-10% w/w of a low viscosity grade hydroxypropyl methylcellulose,
   b) optionally granulating the blend,
   c) lubricating the blend of step a) or granules of step b), and
   d) compressing into or filling into suitable size solid dosage form.
2. The process according to claim 1 wherein drug capable of dissociating as valproate ion is selected from valproic acid and its pharmaceutically acceptable salts, esters, amides and the like.
3. The process according to claim 2 wherein valproic acid salt is divalproex sodium.
4. The process according to claim 3 wherein amount of divalproex sodium may vary from about 10% to about 90% by weight of the total pharmaceutical composition weight.
5. The process according to claim 1 wherein pharmaceutical composition is suitable for once a day dosing.
6. The process according to claim 1 wherein high viscosity grade hydroxypropyl methylcellulose is one whose 2% aqueous solution has nominal viscosity greater than about 10,000 cP.
7. The process according to claim 6 wherein the nominal viscosity is 10,000 to 100,000 cP.
8. The process according to claim 7 wherein the nominal viscosity is 15,000 cP.
9. The process according to claim 1 wherein high viscosity grade hydroxypropyl methylcellulose is present in the concentration range of about 20-40% w/w.
10. The process according to claim 1 wherein low viscosity grade is one whose 2% aqueous solution has nominal viscosity less than about 1, 000 cP.
11. The process according to claim 10 wherein the nominal viscosity is 5 to 100 cP.
12. The process according to claim 11 wherein the nominal viscosity is 5 cP.

13. The process according to claim 1 wherein low viscosity grade hydroxypropyl methylcellulose is selected in the concentration range of 1-5% w/w.
14. The process according to claim 1 wherein pharmaceutical composition is selected from tablet, capsule and the like.
15. The process according to claim 1 wherein pharmaceutical composition is tablet.
16. The process according to claim 1 wherein extended release pharmaceutical composition further comprises pharmaceutically inert excipients.
17. The process according to claim 16 wherein pharmaceutically inert excipients is selected from the group comprising of glidants, lubricants, diluents and binders, and the like.
18. The process according to claim 1 wherein granulation is carried out by a process selected from wet granulation, dry granulation, melt extrusion techniques and the like.
19. The process according to claim 18 wherein granulation is carried out by wet granulation technique.
20. The process for the preparation of an extended release pharmaceutical composition according to claim 19 wherein wet granulation comprises the steps of
    a) dry blending a mixture of a drug capable of dissociating as valproate ion, and high viscosity grade hydroxypropyl methylcellulose and a low viscosity grade hydroxypropyl methylcellulose;
    b) wet granulating the blend from step a);
    c) drying and sizing the wet granules;
    d) lubricating the granules from step c);
    e) compressing into or filling into suitable size solid dosage form; wherein all weight percentages are based upon the total weight of the dosage form.
21. The process for the preparation of an extended release pharmaceutical composition according to claim 20 wherein in step e) granules are compressed into solid dosage form.
22. The process for the preparation of an extended release pharmaceutical composition according to claim 20 and 21 wherein solid dosage form is tablet.

23. The process for the preparation of an extended release pharmaceutical composition according to claim 20 wherein in step e) granules are filled into suitable size solid dosage form.

24. The process for the preparation of an extended release pharmaceutical composition according to claim 20 and 23 wherein solid dosage form is a capsule.

25. The process for preparation of an extended release pharmaceutical composition according to claim 1 wherein it is used for treatment of epilepsy, migraine and bipolar disorders.

26. A process for the preparation of an extended release pharmaceutical composition comprising the steps of-

a) blending a drug capable of dissociating as valproate ion, from 15-50% w/w of a high viscosity grade hydroxypropyl methylcellulose and from 0.1-10% w/w of a low viscosity grade hydroxypropyl methylcellulose,

b) optionally granulating the blend,

c) lubricating the blend of step a) or granules of step b), and

d) compressing into or filling into suitable size solid dosage form

wherein the composition is free of microcrystalline cellulose.

27. The process according to claim 26 wherein drug capable of dissociating as valproate ion is selected from valproic acid and its pharmaceutically acceptable salts, esters, amides and the like.

28. The process according to claim 27 wherein valproic acid salt is divalproex sodium.

29. The process according to claim 28 wherein amount of divalproex sodium may vary from about 10% to about 90% by weight of the total pharmaceutical composition weight.

30. The process according to claim 26 wherein pharmaceutical composition is suitable for once a day dosing.

31. The process according to claim 26 wherein high viscosity grade hydroxypropyl methylcellulose is one whose 2% aqueous solution has nominal viscosity greater than about 10,000 cP.

32. The process according to claim 31 wherein the nominal viscosity is 10,000 to 100,000 cP.
33. The process according to claim 32 wherein the nominal viscosity is 15,000 cP.
34. The process according to claim 26 wherein high viscosity grade hydroxypropyl methylcellulose is present in the concentration range of about 20-40% w/w.
35. The process according to claim 26 wherein low viscosity grade is one whose 2% aqueous solution has nominal viscosity less than about 1,000 cP.
36. The process according to claim 35 wherein the nominal viscosity is 5 to 100cP.
37. The process according to claim 36 wherein the nominal viscosity is 5 cP.
38. The process according to claim 26 wherein low viscosity grade hydroxypropyl methylcellulose is selected in the concentration range of 1-5% w/w.
39. The process according to claim 26 wherein pharmaceutical composition is selected from tablet, capsule and the like.
40. The process according to claim 26 wherein pharmaceutical composition is tablet.
41. The process according to claim 26 wherein extended release pharmaceutical composition further comprises pharmaceutically inert excipients.
42. The process according to claim 41 wherein pharmaceutically inert excipients is selected from the group comprising of glidants, lubricants, diluents and binders, and the like.
43. The process according to claim 26 wherein granulation is carried out by a process selected from wet granulation, dry granulation, melt extrusion techniques and the like.
44. The process according to claim 43 wherein granulation is carried out by wet granulation technique.
45. The process for the preparation of an extended release pharmaceutical composition according to claim 44 wherein wet granulation comprises the steps of
    a) dry blending a mixture of a drug capable of dissociating as valproate ion, and high viscosity grade hydroxypropyl methylcellulose and a low viscosity grade hydroxypropyl methylcellulose;
    b) wet granulating the blend from step a);
    c) drying and sizing the wet granules;

d) lubricating the granules from step c);

e) compressing into or filling into suitable size solid dosage form; wherein all weight percentages are based upon the total weight of the dosage form.

46. The process for the preparation of an extended release pharmaceutical composition according to claim 45 wherein in step e) granules are compressed into solid dosage form.

47. The process for the preparation of an extended release pharmaceutical composition according to claim 45 and 46 wherein solid dosage form is tablet.

48. The process for the preparation of an extended release pharmaceutical composition according to claim 45 wherein in step e) granules are filled into suitable size solid dosage form.

49. The process for the preparation of an extended release pharmaceutical composition according to claim 45 and 48 wherein solid dosage form is a capsule.

50. The process for preparation of an extended release pharmaceutical composition according to claim 26 wherein it is used for treatment of epilepsy, migraine and bipolar disorders.

51. The process for preparation of extended release pharmaceutical composition as per the examples and specifications described herein.

Dated **17TH** day of **February, 2004.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

A PROCESS FOR PREPARATION OF AN EXTENDED RELEASE FORMULATION OF DIVALPROEX

The present invention relates to a process for the preparation of an extended release pharmaceutical composition comprising a drug capable of dissociating as valproate ion, a high viscosity grade hydroxypropyl methylcellulose and a low viscosity grade hydroxypropyl methylcellulose.